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Short title running head: A multivariable model to predict foot ulceration

The development and validation of a multivariable prognostic model to predict foot ulceration in diabetes using a systematic review and individual patient data meta-analyses

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What's new?

- Cohort studies to identify risk factors for foot ulceration in people with diabetes have been published in the biomedical literature since the early 1990s.
- We assembled an international data set of risk factors collected from 16 385 individuals with diabetes who took part in cohort studies to derive and validate a

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prognostic model of three risk factors: a history of foot ulceration, an inability to feel a 10 g monofilament and at least one absent pedal pulse.

- The use of only these three risk factors in foot risk assessments during annual diabetes foot checks could reduce the amount of time spent assessing risk and thereby increase the number of people with diabetes who have checks performed.
- The frequency of risk assessment should be considered in future research.

Abstract

Aims Diabetes guidelines recommend screening for the risk of foot ulceration but vary substantially in the underlying evidence base. Our purpose was to derive and validate a prognostic model of independent risk factors for foot ulceration in diabetes using all available individual patient data from cohort studies conducted worldwide.

Methods We conducted a systematic review and meta-analysis of individual patient data from 10 cohort studies of risk factors in the prediction of foot ulceration in diabetes. Predictors were selected for plausibility, availability and low heterogeneity. Logistic regression produced adjusted odds ratios (ORs) for foot ulceration by ulceration history, monofilament insensitivity, any absent pedal pulse, age, sex and diabetes duration.

Results The 10 studies contained data from 16 385 participants. A history of foot ulceration produced the largest OR [6.59 (95% CI 2.49 to 17.45)], insensitivity to a 10 g monofilament [3.18 (95% CI 2.65 to 3.82)] and any absent pedal pulse [1.97 (95% CI 1.62 to 2.39)] were consistently, independently predictive. Combining three predictors produced sensitivities between 90.0% (95% CI 69.9% to 97.2%) and 95.3% (95% CI 84.5% to 98.7%); the corresponding specificities were between 12.1% (95% CI 8.2% to 17.3%) and 63.9% (95% CI 61.1% to 66.6%).

Conclusions This prognostic model of only three risk factors, a history of foot ulceration, an inability to feel a 10 g monofilament and the absence of any pedal pulse, compares favourably with more complex approaches to foot risk assessment recommended in clinical diabetes guidelines.

<H1>Background

Diabetes-related lower extremity amputations and foot ulcers cause considerable morbidity, more than double the rate of mortality and generate a high monetary cost for health and social care systems [1,2]. The high prevalence of diabetes and increasing incidence in many developing countries mean this complication is likely to become more burdensome.

Across the globe, clinical guidelines for diabetes recommend screening for the risk of foot ulceration but individual guidelines vary substantially in the evidence used to support recommendations with many based on clinical consensus [3–8]. The consequence of this situation is a wide variation in the clinical symptoms, signs and tests that health professionals use to identify a person's risk of foot ulceration. Moreover, because foot risk assessment tools are often derived in people at high risk of ulceration [9,10], they may not perform well in people whose risk is low. Because some of the recommended tools require expensive equipment and clinically time-consuming procedures there is likely to be considerable value in the identification of a simple, evidence-based, risk assessment tool with high prognostic value.

Our purpose was to derive and validate a prognostic model of independent risk factors for foot ulceration in diabetes using all available individual patient data (IPD) from cohort studies conducted worldwide to inform the development of an evidence-based clinical prediction rule [11,12].

<H1>Methods

We undertook a systematic review and meta-analyses of IPD collected in cohort studies of predictive factors for foot ulceration in diabetes (PROSPERO no: CRD42011001841). Ethical approval was not required because the data were anonymized, already published and in the public domain [13,14].

Included studies had to recruit people with a diagnosis of diabetes who were free of foot ulceration, or whose authors could provide separate data from those who did not have ulceration at recruitment. The outcome of interest was foot ulceration.

<H2>The review eligibility criteria

People aged 18 years old and over, with a diagnosis of diabetes (Type 1 or Type 2), with at least one foot, who were free of ulceration at the time of entry to a cohort study with ulceration as the outcome variable.

<H2>Search strategies

Electronic searches were conducted in MEDLINE and Embase databases from inception to August 2017 (MEDLINE) and June 2017 (Embase). One reviewer applied the review eligibility criteria to the full-text articles and a second reviewer checked a 10% random sample to ensure that no eligible studies were missed.

<H2>Quality assessment

We compiled a list of items relevant to our review question sourced from published quality assessment checklists for cohort studies [14].

<H2>Development of the model

Data were cleaned, and extreme values checked with the authors. Where there were missing data, discussions to understand the pattern of missingness took place. We included variables for which the greatest amount of data from several sources were available. Variables had to

have been collected in at least three data sets; be defined consistently across data sets (or be able to be recoded) and the extent of heterogeneity should not be so large as to invalidate the meta-analysis.

A univariate logistic regression analysis was performed to obtain odds ratios (ORs) using all variables which met our criteria. The ORs were examined in forest plots to assess heterogeneity, then those variables thought to be clinically important, biologically plausible, and easy to measure in clinical practice were considered by the whole research team.
For data from a particular study to be included in the model it must have a complete set of these variables. There was a trade-off between the number of variables and the number of studies that were included, with more variables leading to fewer studies because of lack of additional variables in study data sets.

<H2>Primary statistical analysis

A multivariable model was fitted using the core variables of the primary model in each separate cohort study using logistic regression with first incident foot ulceration as the binary outcome. We did not analyse predictors of recurrent ulceration. We adjusted the ORs from each study with the same set of predictors [17–19]. These were included in meta-analyses using a random effects model by the generic inverse method and heterogeneity was assessed using I^2 and tau-statistics [20]. We conducted the analyses first using patient data from the total population regardless of previous history of foot ulceration and a second analysis using only data from people with no previous history of foot ulceration to check whether the same variables were predictive in both groups. Our approach to a planned survival analysis deviated from our published protocol in that we performed a two-step meta-analyses because the largest cohort study (n = 6603) [21] had no time-to-ulceration data and another large data set (n = 3412) [22] was only available to the project statisticians via a Safe Haven facility and could not be physically merged with the other data sets for a one-step approach [23].

To validate the final model an independent statistician re-estimated the ORs in a new data set (n =1489) not previously used in our analysis, to allow a comparison of the ORs from our meta-analysis [24].

We calculated sensitivity, specificity and positive and negative likelihood ratios for an inability to feel a 10 g monofilament and/or any absent pedal pulse with ulceration at 1 and 2 years after the risk assessments took place as these tests survived validation. Finally, we calculated these same measures of diagnostic accuracy for the three risk factors that survived validation (the above and history of foot ulceration) for foot ulceration at 1 and 2 years. Heterogeneity was assessed visually with forest plots but not with I^2 or tau-statistics because these are less reliable with small numbers of studies. Logistic regression and meta-analyses were conducted with SAS 9.3 and the meta package in R. Analyses of sensitivity and specificity were all conducted using the DiagMeta package in R (https://cran.r-project.org/).

<H1>Results

We contacted the principal investigators of 17 studies [22–38] that met the eligibility criteria and an agreement to share anonymized data was obtained from 10 [22–24,32–38]. The flow of studies throughout the review and the reasons for exclusion can be found in Fig. S1.

Data from 16 385 people with diabetes were obtained, of these 1221 (7.5%) experienced a foot ulcer (Fig. S2). Authors of eight studies made 'raw' data available [22,32–38] and data from a ninth study were made available via Safe Haven, a data management system with secure and restricted access [23]. Finally, a tenth corresponding author was not granted permission from his Institutional Review Board to share data [24] but was able to contribute to the meta-analysis by subjecting the data from his cohort study to the same analytical procedures as all other studies in our meta-analysis to provide estimates of ORs that externally validated the final model independently. The characteristics of each individual study can be found in Table 1.

The percentage of missing data in the studies included in the final model was < 3% (range 0–2.9%). Eye problems, tuning fork, ankle reflexes, foot deformity, ethnicity, living alone, pin-prick test, temperature test and peak plantar pressure variables were either not collected in a minimum of three studies or were inconsistently measured across studies and it was not possible to standardize them. We chose any absent pedal pulse rather than ankle–brachial indices as a measure of peripheral vascular disease because more studies collected these data. The variables selected for inclusion in the primary model by our international multidisciplinary team were: age, sex, duration of diabetes, prior ulceration or amputation, any absent dorsalis pedis or posterior tibialis pulse on either foot, and insensitivity to 10 g monofilament at any foot site.

<H2>The primary meta-analysis

The results of the univariate and primary multivariable model meta-analyses together with those from the validation analysis are presented in Tables 2 and 3. Forest plots of the pooled ORs with 95% confidence intervals (CIs) are provided for the primary model's predictors in multivariable analyses in Figs 1–3 and S3–S5. The ORs in the multivariable analyses were adjusted for age, sex, duration of diabetes, insensitivity to 10 g monofilament, any absent pedal pulse, and history of foot ulceration.

A history of foot ulceration was found to be predictive of diabetes-related foot ulceration. This effect was also observed in the analyses of the external data set (Fig. 1) (meta-analyses OR 6.59, 95% CI 2.49 to 17.45; validation OR 2.98, 95% CI 2.15 to 4.13).

The 10 g monofilament test was shown to be consistently predictive in the meta-analyses and in the external validation data set (Fig. 2) (meta-analyses OR 3.18, 95% CI 2.65 to 3.82; validation OR 3.49, 95% CI 2.49 to 4.89). Notably the estimated heterogeneity was zero.

The absence of at least one pedal pulse was shown to be predictive in the meta-analyses and the validation data set (Fig. 3) (meta-analyses OR 1.97, 95% CI 1.62 to 2.39; validation OR 2.56, 95% CI 1.22 to 5.36).

The duration of diabetes was not found to be consistently predictive between the meta-analyses of nine studies (Fig. S3) (meta-analyses OR 1.02, 95% 1.01 to 1.04) when compared with the analysis of the validation data set (OR 0.98, 95 CI 0.97 to 0.99)

Age was not found to be predictive of foot ulceration in either the meta-analyses (Fig. S4) or the external validation data set (meta-analyses OR 1.00, 95% CI 0.99 to 1.02; validation OR 0.99, 95% CI 0.98 to 1.01).

Female sex was found to be protective of foot ulceration across studies in the IPD meta-analysis (meta-analyses OR 0.74, 95% CI 0.60 to 0.92) (Fig. S5) but this finding was not replicated in the validation study, which included mostly men.

The ORs calculated from meta-analyses of data from people who had never experienced a foot ulcer did not differ statistically from the analysis of data from the entire study population data except for the variable 'female sex' (Table 3). The results for gender were not statistically significantly different for people who had no history of ulceration (OR 0.84, 95% CI 0.68 to 1.04) but were statistically significantly different in the total population (OR 0.74 (95% CI 0.60 to 0.92), the latter estimate suggesting female gender is protective of foot ulceration in those who have a history of foot ulceration.

The calculation of accuracy measures within 1 and 2 years of assessment using the two risk factors in combination was only possible in three studies because these had ulcers necessary for analyses at 1 and 2 years (n = 1781) [32,33,36]. The estimates of sensitivity, specificity and likelihood ratios for a 10 g monofilament test used alone, the absence of any pedal pulse used alone and the combined use of a 10 g monofilament test and any absent pedal pulse results where one or other of these elements produces a positive result are presented in Table 4. Heterogeneity in the pooled specificity data makes meta-analyses of these data impractical (Figs S6 and S7) hence we report the sensitivities, specificities and likelihood ratios of the three studies individually.

The results from either the 10 g monofilament test or any absent pedal pulse being positive were found to increase the sensitivities in each study, ranging from 74.2% to 95.3% at a cost to the specificities (specificities ranging from 27.1% to 66.3%), the corresponding positive likelihood ratio varied from 1.31 to 2.31 and the negative likelihood ratio from 0.17 to 0.54. (Table 4, Figs S8 and S9).

For each study, no statistically significant differences were found between 1 and 2 years for the majority of measures using the monofilament test or any absent pedal pulse alone or combined. (Table 4).

Estimates of sensitivity and specificity from combining all three risk factors increased the sensitivity and reduced the specificity of the prognostic model at 1 and 2 years after testing (n = 1781). The sensitivity and specificity for a 10 g monofilament test, the absence of any pedal pulse and a history of foot ulceration (where any one of the elements produces a positive result) are presented in Table 5.

Risk assessments with all three risk factors at an interval of 1 year show sensitivities of between 90.0% and 95.3%, while the corresponding specificities were reduced to between 12.1% and 63.8%. Risk assessments at 2-year intervals with the three risk factors in combination showed sensitivities between 90.9% and 95.6% with corresponding specificities reduced to between 13.2% and 63.9% (Table 5). Any absent pulse was found to be more informative than the three-factor model in the population reported by Pham [36].

In one study [33], the three-factor model sensitivity exceeded that of the two-factor model by a statistically significant degree at 2 years (Tables 4 and 5). In another study [36], the three-factor model specificity was statistically significantly lower than that of the two-factor model at both 1 and 2 years (Tables 4 and 5).

<H2>Risk of bias

For the five items used to assess the quality of the conduct of the studies, five studies exhibited a low risk of bias [22,32,33,36,38]. However, the collection of outcomes in a 'blind' manner was a feature of only 50% the studies which exposes some of these data to the threat of investigator bias.

<H1>Discussion

The central importance of foot risk assessment in health checks for people with diabetes is acknowledged by healthcare systems across the world. Our analyses, based on data collected internationally, indicate that only three risk factors, a history of foot ulceration, the inability to feel a 10 g monofilament and the absence of at least one pedal pulse, are required to distinguish between those who will ulcerate and those who will not with a high degree of accuracy comparable with other, more complex, prognostic models [39]. The simplicity of our model has advantages for clinical practice because it is intuitively correct to suppose that the fewer tests and elements from the patient history that healthcare professionals are required to consider, the more likely risk assessment procedures will be performed.

The very large ORs calculated for a history of foot ulceration were perhaps unsurprising and there can be no doubt about the high-risk status of these individuals. However, the most consistent set of results in the meta-analysis were obtained from data for the 10 g monofilament test and this quick, simple and relatively cheap test identified risk in all cohort studies with remarkable consistency. The almost complete absence of heterogeneity in the meta-analyses of monofilament data came from five studies involving 11 522 people from three different countries, and as such was unexpected.

The results for any absent pedal pulse indicate that this sign is also independently predictive of a risk of foot ulceration. Our use of 'any absent pedal pulse' as a measure of PVD may have underestimated the predictive value of vascular disease for foot ulceration. In a study of major vascular outcomes in people with Type 2 diabetes, every additional absent pedal pulse resulted in a proportional increase in the hazard ratios [40].

Adding the palpation of any absent pedal pulse to an inability to feel a 10 g monofilament increases sensitivity at 1- and 2-year intervals. When two and three factors were combined, higher levels of sensitivity, but correspondingly lower levels of specificity, were observed. This is because any two tests combined with a Boolean OR are bound to increase sensitivity at the expense of specificity. Whether this is acceptable depends on the clinical context [41] but in this scenario the consequences of failing to detect a person at risk of foot ulceration (false negatives) may be potentially far more serious than the increased routine healthcare costs associated with false-positive results from a test with lower specificity. The high levels of sensitivity for the combined models support the extension of screening intervals beyond the conventional 1 year in those who test negative (i.e. do not exhibit either two or three risk factors).

The variation in the accuracy of the two- and three-factor models in the two smaller studies deserves consideration. The heterogeneity in the effects of predictive models can arise from differences in disease spectrum, populations, settings, timing and the prevalence of the disease or outcome (incidence) [42,43]. The ulcer incidence was higher in two studies [33,36], as was the number of re-ulcerations, compared with the population described by Crawford (Table 1) [32]. The worse foot pathology of these people may also explain the likelihood ratios obtained for these two cohorts which indicate that the informative value of the models is low [44].

The number of years that a person has had a diagnosis of diabetes was found to be a risk factor, but there is a high level of heterogeneity in the meta-analyses and this finding was not confirmed in the validation analysis. Female sex seems to confer some protection against ulceration and this might relate to a greater propensity for self-care and attention to foot health among the women in the study populations [45], or reflect other physiological or behavioural differences relating to sex. Sex was not validated as a significant predictor in the validation data set, which had a predominantly male population [24].

The quality of the conduct of the 10 studies included in the systematic review was assessed as high. Only one item was found to threaten the validity of the included studies: the blinding of the individuals who ascertained the outcome variable (ulceration) was only maintained in 50% of the included studies [22,32,33,36,38]. This is widely believed to be an important quality factor in prognostic studies and clinical prediction rules [46,47]. However, the meta-analyses upon which our conclusions are based included only one study [23] in which the investigators knew the status of the index test results for some cases and the estimates these data contribute only differ statistically from pooled estimates for one prognostic factor – previous history of ulceration or amputation. This may result from the inherent difference in study design, being the only study to use routinely collected data.

<H2>Strength and limitations of the results

Our externally validated prognostic model for foot ulceration in diabetes used all obtainable IPD from global cohort studies and the analysis is based on data from 11 816 people with diabetes, the largest of its kind. The differences in the demographics of the included populations, the international and clinical settings in which the data were collected and the variety of health care professionals who undertook the foot assessments mean the findings have good external validity. That our international, multidisciplinary group of individuals considered the most clinically useful variables for inclusion in a prognostic model helped ensure that all clinical perspectives and expertise were represented.

The main limitation of the work is that the model results are expressed as summary ORs, which do not readily allow clinicians to assess risk and our research is on-going to produce a clinical prediction rule with a simple scoring system based on calculated relative risks from a sample of these data. From these we plan to produce risk categories and assess the performance of the clinical prediction rule by analysing its properties of discrimination and calibration [48]. The lack of data for systemic conditions such as stroke or coronary heart disease is also a limitation; all three risk factors in our model are intrinsic to the foot and none are suitable for self-care. Furthermore, the small number of studies (n = 3) included in the analysis of accuracy measures of the model means these estimates of diagnostic accuracy should be interpreted with caution.

<H2>Implications for policy, practice and research

Given the increased worldwide prevalence in diabetes, a clinical prediction rule based on data collected globally and involving only three risk factors that are easy to measure could lead to more people with diabetes having foot ulcer risk assessments and improved outcomes. The duration of the screening interval should be the focus of future research for this simplified prognostic model.

<H1>Conclusions

This systematic review and meta-analysis of IPD collected worldwide has produced a simple prognostic model of three risk factors that are independently predictive of foot risk ulceration in diabetes. Although an even simpler model appeared more suitable for use in a speciality foot clinic, the informative value of re-testing people with a history of foot ulceration is questionable. The prognostic utility of a history of foot ulceration, an inability to feel the 10 g monofilament and at least one absent pedal pulse indicates that the implementation of such a simplified approach to annual diabetes foot checks could reduce the amount of clinical time spent testing and thereby permit more people with diabetes to be classified for risk of foot ulceration and potentially lead to more effective prevention.

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Competing interests

None declared.

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Contributors

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FIGURE 1 Author to supply caption.

FIGURE 2 Author to supply caption.

FIGURE 3 Author to supply caption.

<H1>Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow diagram of studies in the individual patient data systematic review.

Figure S2. Flow diagram of people in the individual patient data meta-analysis.

Figure S3. Author to supply caption.

Figure S4. Author to supply caption.

Figure S5. Author to supply caption.

Figure S6. Author to supply caption.

Figure S7. Author to supply caption.

Figure S8. Author to supply caption.

Figure S9. Author to supply caption.

Table 1 Key elements of included studies

Author (date)	Inclusion/exclusion	Derivation/validation study. Recruitment dates/duration of follow-up	Setting	Origin of the data	Who took the measurements	Types and number of events in participants
Abbott (2002)	Type 1 or 2 diabetes	Derivation study April 1994 to 1996 2 years	GP practices Diabetes centres Hospital outpatients Podiatry clinics in North West UK	Consultation and examinations	Podiatrists and research nurses	Participants = 6603 Ulcers =291 Re-ulcerations=186 Amputations = 27 Deaths = 0
Boyko (2006)	Inclusion: all general internal medicine clinic patients with diabetes Exclusion: current foot ulcer, bilateral foot amputations, wheelchair use or inability to ambulate, illness too severe to participate, or psychiatric illness that prevented informed consent.	Derivation study Recruitment initiated in 1990 on a continuous basis until end of follow-up on 31 October 2012. Mean duration of follow-up 48.7 months	The general internal medicine clinic of a single Department of Veterans Affairs Medical Center	Consultations in specialized foot research clinic whose sole purpose was the collection of data for this research	Two nurse practitioners and two technicians who worked full-time for this research	Participants = 1489 Ulcers = 229 Re-ulcerations = 51 Amputations = 50 Deaths = 121
Crawford (2011)	≥ 18 years of age, diagnosis of diabetes, ambulant, free of foot ulceration and able to give informed consent	Derivation study March 2006 to June 2007 11.4 months	32 podiatry clinics in primary care settings in Tayside Scotland, UK	Consultations and examinations Events ascertained from patient paper records by individual blind to test results	8 podiatrists	Participants = 1193 Ulcers =23 Re-ulcerations = 8 Amputations = 0 Deaths = 59
Kastenbauer (2001)	Exclusion/inclusion criteria: Inclusion: Type 2	Derivation study January 1994 to 1995	Diabetes centre with in a hospital in Vienna, Austria	Consultation and examinations	2 biologists who worked in the field of diabetes foot research and	Participants = 187 Ulcers =18 in 10 participants

	diabetes in men and women < 75 years old; with normal gait pattern and plantar pressure could be reliably measured Exclusion: past or current foot ulcers, lower extremity amputation, severe peripheral arterial disease, severe neurological deficits due to other diseases than diabetes, and Charcot's foot	Mean 3.6 years			diabetologist, who was responsible for the diabetic foot clinic	Re-ulcerations = data not collected Amputations =3 Deaths = 9
Leese (2011)	Inclusion: all people with diabetes and on the diabetes register who had undergone foot risk assessment during 2004–2006	Derivation study 2004 to 2006 1.19 ± 0.91	Community and hospital diabetes foot clinics in Tayside, UK	Routinely collected clinical information (regional diabetes electronic register) Linked data Same electronic records The local multidisciplinary foot clinic and community and hospital podiatry paper records (for ascertaining events)	Any GP, podiatrist nurse of specialist caring for people with diabetes	Participants =3412 Ulcers = 322 Re-ulcerations = 150 Amputations =55 Deaths =575
Monami (2009)	Inclusion; Type 2 diabetes outpatients referred the diabetes clinic of the geriatric unit.	Derivation study December 1995 to December 2000 4.2 ± 2.2 years	Diabetic clinic of the geriatric unit of a hospital, Florence, Italy	Consultation Ulcer ascertained by routinely collected data	Diabetologists and research fellows	Participants =1944 Ulcers=91 Re-ulcerations = 38 Amputations =0

						Deaths =321
Monteiro-Soares (2010)	Diabetes mellitus Exclusion: unable to walk, data incomplete or fewer than 3 podiatry appointments	Validation study February 2002 to October 2008 25 months (range 3–86)	A public tertiary hospital, Vila Nova de Gaia, Portugal	Consultation (interview and foot exam) Medical records for both predictive and outcome variables	2 podiatrists with 6 and 10 years' experience in the management of the diabetic foot	Participants = 360 Ulcers =94 Re-ulcerations = 69 Amputations =0 Deaths = 0
Pham (2000)	Diabetes mellitus who attended one of three large diabetic foot centres. Diabetes diagnosis confirmed by primary care provider	Derivation study January 1995 to January 1996 Followed up for 30 months (range 6–40)	3 large diabetic foot centres, USA	Consultation interview and exam	Podiatrists	Participants = 248 Ulcers =73 Re-ulcerations= 32 Amputations =0 Deaths = 13
Rith-Najarian (1992)	On diabetes register and had an annual foot exam	Derivation study July 1988 to February 1991 Follow-up 32 months	Primary care setting Native American reservation, USA	Consultation	Physical therapist and a physician	Participants =358 Ulcers = 38 Re-ulcerations = 22 Amputations =14 Deaths = 19
Young (1994)	At least one pedal pulse, no history of ulceration	Derivation study April 1988 to March 1989 Follow-up	Foot clinic in diabetes centre	Consultation Medical patient notes for ascertainment of ulcers	A physician	Participants =592 Ulcers =47 Re-ulcerations =0 Amputations =0 Deaths = 8

Table 2 Pooled estimates of association between the predictors and foot ulceration in the univariate (unadjusted) analysis

New ulcer predictor	*N*	Odds ratio (95% confidence interval)	I_2 (%); tau (level of heterogeneity)
Age	14 823	1.02 (1.01 to 1.03)	26.7; 0
Sex (women v men)	14 895	0.59 (0.47 to 0.74)	46.8; 0.44
Weight	1965	1.01 (0.996 to 1.02)	16.1; 0
Height	2030	1.05 (1.03 to 1.06)	0; 0
BMI	6662	0.98 (0.97 to 1.00)	0; 0
Smoking (yes/no)	12 522	0.96 (0.83 to 1.12)	0; 0
No. of cigarettes per day	6222	1.02 (0.99 to 1.05)	60.9; 0.001
Alcohol (yes/no)	8193	0.92 (0.59 to 1.43)	38.8; 0.08
Alcohol units per week	3786	1.01 (1.00 to 1.02)	0; 0
HbA_{1c} (mmol/mol (%))	7119	1.20 (1.10 to 1.30)	50; 0
Insulin treatment	10 869	1.75 (1.17 to 2.62)	71.5; 0.16
Diabetes duration	14 199	1.05 (1.03 to 1.07)	81.7; 0
Eye problem (yes/no)	8099	2.49 (1.99 to 3.15)	0; 0
Retinopathy	2724	2.09 (.55 to 2.82)	0; 0
Kidney problems	12 438	1.83 (1.18 to 2.83)	60.5; 0
Inability to feel 10g monofilament	12 030	5.61 (4.47 to 7.04)	37.1; 0.027
Any absent pedal pulse	12 327	3.47 (2.32 to 5.21)	80; 0.181

Abnormal vibration perception threshold (VPT)	10 336	7.61 (3.82 to 15.16)	82.5; 0.516
Absent ankle reflex	7879	2.10 (0.71 to 6.22)	89.1; 0.808
Abnormal ankle–brachial index (ABI)	1868	1.836 (0.99 to 3.41)	30.4; 0.124
Any foot deformity	12 093	3.171 (2.16 to 4.65)	57.2; 0.114
History of foot ulceration	14 656	13.74 (6.60 to 28.58)	93.7; 1.022
Previous amputation	11 762	10.31 (4.93 to 21.56)	76.5; 0.469
History of foot ulceration or lower limb amputation	14 709	13.18 (6.56 to 26.51)	93.4; 0.923

Table 3 Comparison of results between the primary multivariable model meta-analysis and the external validation data set

Predictor	Source	Odds ratio	95% CI
History of foot ulceration	Meta-analysis of all data	6.59	2.49 to 17.5
	Boyko validation data set	2.98	2.15 to 4.14
Inability to feel a 10 g monofilament	Meta-analysis of all data	3.18	2.65 to 3.82
	Meta-analysis of data from pts with no history	3.44	2.77 to 4.26
	Boyko validation data set	3.49	2.49 to 4.90
Any absent pedal pulse	Meta-analysis of all data	1.97	1.62 to 2.39
	Meta-analysis of data from pts with no history	2.61	1.81 to 3.75
	Boyko validation data set	2.56	1.22 to 5.36
Sex (female)	Meta-analysis of all data	0.74	0.60 to 0.92
	Meta-analysis of data from pts with no history	0.84	0.68 to 1.04
	Boyko validation data set	1.49	0.42 to 5.32
Duration of diabetes	Meta-analysis of all data	1.02	1.01 to 1.04
	Meta-analysis of data from pts with no history	1.03	1.02 to 1.04
	Boyko validation data set	0.98	0.97 to 0.99

Age	Meta-analysis of all data	1.00	0.99 to 1.02
	Meta-analysis of data from pts with no history	1.01	0.995 to 1.02
	Boyko validation data set	0.99	0.98 to 1.01

Table 4 Estimates of sensitivity, specificity and likelihood ratios at 1 and 2 years for the inability to feel a 10 g monofilament alone, at least one absent pedal pulse alone and inability to feel a 10 g monofilament OR at least one absent pedal pulse based on three cohort studies with time-to-event data (n = 1781). Participant is test positive if any of the risk factors is positive, and negative otherwise

Study	Test	Timepoint (year)	% Sensitivity (95% CI)	% Specificity (95% CI)	Positive likelihood ratio	Negative likelihood ratio
Crawford	Monofilament OR Any absent pedal pulse	1	77.8 (54.8, 91.0)	66.3 (63.6, 69.0)	2.31 (1.78, 3.00)	0.34 (0.14, 0.80)
	Monofilament OR Any absent pedal pulse	2	81.8 (61.5, 92.7)	66.6 (63.8, 69.2)	2.45 (1.98, 3.03)	0.27 (0.11, 0.66)
	Monofilament	1	50.0 (29.0, 71.0)	77.9 (75.4, 80.2)	2.26 (1.41, 3.63)	0.64 (0.40, 1.02)
	Monofilament	2	59.1 (0.39, 0.77)	78.1 (75.7, 80.4)	2.70 (1.88, 3.89)	0.52 (0.32, 0.87)
	Any absent pedal pulse	1	66.7 (43.7, 83.7)	81.9 (79.6, 84.0)	3.69 (2.60, 5.22)	0.41 (0.21, 0.78)

	Any absent pedal pulse	2	59.1 (38.7, 76.7)	81.9 (79.6, 84.0)	3.27 (2.26, 4.73)	0.50 (0.30, 0.83)
Monteiro	Monofilament OR Any absent pedal pulse	1	74.2 (56.8, 86.3)	47.7 (42.4, 53.1)	1.42 (1.13, 1.79)	0.54 (0.30, 0.99)
	Monofilament OR Any absent pedal pulse	2	70.6 (57.0, 81.3)	48.5 (43.0, 54.1)	1.37 (1.12, 1.69)	0.61 (0.39, 0.94)
	Monofilament	1	54.8 (37.8, 70.8)	54.7 (49.3, 60.0)	1.21 (0.86, 1.70)	0.83 (0.55, 1.23)
	Monofilament	2	54.9 (41.4, 67.7)	55.3 (49.8, 60.8)	1.23 (0.93, 1.62)	0.82 (0.59, 1.12)
	Any absent pedal pulse	1	38.7 (23.7, 56.2)	81.5 (76.9, 85.3)	2.09 (1.27, 3.43)	0.75 (0.57, 1.00)
	Any absent pedal pulse	2	31.4 (20.3, 45.0)	81.6 (76.9, 85.5)	1.70 (1.06, 2.72)	0.84 (0.69, 1.02)
Pham	Monofilament OR Any absent pedal pulse	1	95.3 (84.5, 98.7)	27.1 (21.4, 33.7)	1.31 (1.18, 1.46)	0.17 (0.04, 0.68)
	Monofilament OR Any absent pedal pulse	2	89.7 (80.2, 94.9)	28.2 (22.0, 35.3)	1.25 (1.10, 1.41)	0.37 (0.17, 0.77)
	Monofilament	1	95.3 (84.5, 98.7)	28.6 (22.8, 35.3)	1.34 (1.20, 1.49)	0.16 (0.04, 0.64)
	Monofilament	2	89.7 (80.2,	29.9 (23.6,	1.28 (1.13,	0.34 (0.17,

		94.9)	37.1)	1.45)	0.72)
Any absent pedal pulse	1	27.9 (16.7, 42.7)	88.4 (83.3, 92.2)	2.42 (1.31, 4.47)	0.84 (0.67, 0.99)
Any absent pedal pulse	2	25.0 (16.2, 36.4)	89.7 (84.2, 93.4)	2.42 (1.33, 4.41)	0.84 (0.72, 0.97)

Table 5 Estimates of sensitivity and specificity for the inability to feel a 10 g monofilament, at least one absent pedal pulse alone and a history of foot ulceration combined at 1- and 2-year follow-ups based on three cohort studies with time-to-event data. Patient is test positive if any of the risk factors is positive, and negative otherwise. Meta-analysis not performed because of high levels of heterogeneity in the estimates of specificity

Study	Test	Time point	% Sensitivity (95% CI)	% Specificity (95% CI)	Positive likelihood ratios (95% CI)	Negative Likelihood ratios (95% CI)
Crawford (2011)	Three predictors	1	90.0 (69.9, 97.2)	63.8 (61.0, 66.5)	2.48 (2.11, 2.93)	0.16 (0.04, 0.58)
	Three predictors	2	90.9 (72.2, 97.5)	63.9 (61.1, 66.6)	2.52 (2.16, 2.93)	0.14 (0.04, 0.53)
Monteiro-Soares (2010)	Three predictors	1	94.1 (80.9, 98.4)	39.6 (34.4, 45.0)	1.56 (1.38, 1.76)	0.15 (0.04, 0.57)
	Three predictors	2	94.2 (84.4, 98.0)	41.6 (36.2, 47.1)	1.61 (1.44, 1.81)	0.14 (0.05, 0.42)
Pham (2000)	Three predictors	1	95.3 (84.5, 98.7)	12.1 (8.2, 17.3)	1.08 (0.997, 1.18)	0.39 (0.10, 1.57)
	Three predictors	2	95.6 (87.8, 98.5)	13.2 (09.0, 19.1)	1.10 (1.02, 1.19)	0.33 (0.10, 1.08)

Table 6. Risk of bias within the included studies.

	Were a consecutive sample of people recruited?	Was the timing of the follow-up long enough for an ulcer to develop?	Can the test be replicated from the description in the published report?	Were the investigators who collected the outcomes blind to the results of the index tests?	Has the study size been fully justified?
Abbott (2002)	Y	Y	Y	Y	N
Boyko (2006)	Y	Y	Y	N	Y
Crawford (2011)	Y	Y	Y	Y	Y
Kastenbauer (2001)	Y	Y	Y	N	N
Leese (2011)	Y	Y	Y	N	N
Monami (2009)	Y	Y	Y	N	N
Monterio-Soares	Y	Y	Y	Y	N
Pham (2000)	Y	Y	Y	Y	N
Rith-Najarian (1992)	N	Y	Y	N	N
Young (1994)	Y	Y	Y	Y	N